REMARKS

Claims 40-47 and 50-52 are presented for continued examination. Applicants respond below to the specific rejections raised by the PTO in the Final Office Action mailed August 24, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of the Claim Status

The Examiner noted that Claims 46 and 47 were not indicated as being "Currently Amended" in Applicants' Amendment and Response dated July 26, 2004. Applicants herein resubmit the previous listing of the claims with their correct status. Please note that these claims are identical to those submitted by Applicants in their Response filed on July 26, 2004. The Applicants have not further amended the claims or added new claims in response to the Final Office Action dated August 24, 2004.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 40-47 and 50-52 under 35 U.S.C. § 101 for lacking patentable utility. More specifically, the PTO alleges that the invention lacks any apparent or disclosed, specific and substantial, credible utility. Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly

is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, *emphasis* added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only

after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Specific, Substantial, and Credible Utility

The PTO asserts that the invention allegedly lacks substantial utility because the claims are drawn to polypeptides (PRO444) having, as of yet, an undetermined function or biological significance. More specifically, the PTO argues that evidence in the specification that PRO444 polypeptides are capable of inducing the expression of c-fos in pericyte cells, is not sufficient to adequately support the asserted utilities of diagnosing and treating tumors, and stimulating angiogenesis under 35 U.S.C. §101.

Applicants respectfully disagree. While 35 U.S.C §101 only requires that one specific, substantial, and credible utility be either asserted or well established, the specification provides at least three asserted utilities for the claimed PRO444 polypeptides. The first two disclosed utilities are that PRO444 polypeptides induce the expression of c-fos in pericyte cells, and therefore, are useful not only as diagnostic markers for pericyte associated tumors, but also for giving rise to antagonists that are useful for the therapeutic treatment of pericyte associated tumors. Specific antagonists include antibodies, for example. Thus the first two disclosed utilities relate to pericyte tumor diagnosis and treatment. Furthermore, as c-fos expression induces angiogenesis, the third asserted utility is that PRO444 polypeptides are useful in stimulating angiogenesis. Inducing angiogenesis could be beneficial for patients in need of wound healing, for example.

As the assertion of a utility creates a presumption of utility sufficient to satisfy 35 U.S.C. §101, the burden is on the Examiner to prove that it is more likely than not that a skilled artisan would doubt the truth of the statement of utility. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

The PTO has attempted to rebut the presumption of utility by relying on three references (cited in the previous Office Action mailed April 27, 2004) to support its position that c-fos expression represents a general cellular response to a variety of stimuli. Based on these cited references, the PTO concludes that "the art clearly recognizes that induction of c-fos expression represents a general non-specific first line of cellular response to a variety of stimuli in a variety of cells, one skilled in the art would not attribute the induction of c-fos expression in pericytes by the instant polypeptides as a physiological reaction specifically induced by these particular polypeptides." (Final Office Action, August 24, 2004, pages 3 and 4)

Applicants respectfully disagree with the PTO's position and submit herewith the Declaration of Dr. Mary Gerritsen, P.h.D., one of the inventors of the present invention, that describes in detail the results and significance of the c-fos induction assay on pericytes, "Assay 93", which is described in Example 60 on page 142 of the specification. (Declaration ¶ 5) This declaration establishes the specific, substantial, and credible utility of the claimed PRO444 polypeptide.

Assay 93 is an assay designed to determine whether particular compounds are capable of stimulating retinal pericytes through the c-fos pathway. (Declaration ¶ 6) Retinal pericytes are unique cells that play an important role in regulating angiogenesis. (Declaration ¶ 6) More specifically, pericytes help regulate capillary permeability and stabilize newly formed blood vessels. (Declaration ¶ 6) C-fos is a transcription factor involved in the regulation of cellular growth, including cancer and angiogenesis. (Declaration ¶ 6) Growth factors capable of stimulating pericytes signal through the c-fos pathway. (Declaration ¶ 6)

In light of their significant relationship with angiogenesis and cancer, it is useful to identify compounds capable of stimulating pericytes through the c-fos pathway in order to treat, promote and diagnose these conditions. (Declaration ¶ 7) Furthermore, one with skill in the art would reasonably conclude that the presence or overexpression of a compound capable of inducing c-fos expression in pericytes (*e.g.,* PRO444) in a subject would more likely indicate the onset of cancer and/or angiogenesis as opposed to a subject who lacked this polypeptide. (Declaration ¶ 7) Likewise, a skilled artisan would also reasonably conclude that neutralizing

compounds capable of stimulating c-fos expression in pericytes (*e.g.*, PRO444) could be useful in preventing the onset and/or progression of cancer and/or angiogenesis. (Declaration ¶ 7)

In Assay 93, 646 samples representing 382 different compounds were tested for their ability to induce c-fos expression in pericytes. (Declaration ¶ 10) The tested compounds included many known cytokines (*e.g.*, Interleukin-1, tumor necrosis factor, interferon), growth factors (*e.g.*, vascular endothelial growth factor, fibroblast growth factor, epidermal growth factor), chemokines, autocoids (e.g. endothelin), hormones (e.g. glucagons, luteinizing hormone) and polypeptides of unknown function. (Declaration ¶ 10) Of the 646 different samples that were assayed, only 48 tested positive for inducing c-fos expression in pericyte cells. (Declaration ¶ 10) Several of the 48 samples testing positive represented different lots of the same compound. (Declaration ¶ 10) As very few of the tested compounds were able to induce c-fos expression, it can be reasonably concluded from these results that the stimulation of c-fos in pericytes is not a generalized response. (Declaration ¶ 10)

The Examiner's position that c-fos induction in pericytes is a generalized response is based on the teachings of three journal articles. More specifically, the Examiner cited: Janknecht et al., *Carcinogenesis*, vol. 16 no. 3, pp. 443-450 (1995), Herrera et al., *Progress in Neurobiology,* vol. 50, pp. 83-107 (1996), and Kovács, *Neurochem Int.* vol. 33, pp. 287-297 (1998) to support the assertion that c-fos induction is a "non-specific first line of cellular response" and that PRO444 accordingly lacks sufficient utility. (See previous Office Action April 27, 2004, page 5) It is important to note that none of these three articles discuss whether c-fos induction in pericyte cells is a general response. (Declaration ¶ 9) For example Kovács is directed to c-fos induction in neuronal cells, and Herrera et al. is directed to c-fos expression in brain cells. (Declaration ¶ 9) Accordingly, the teachings of these articles regarding c-fos induction are not necessarily applicable to pericytes, the specific cell type tested in Assay 93. (Declaration ¶ 9) As mentioned above, the results of Assay 93 indicate that the induction of c-fos in pericytes is not a generalized response. (Declaration ¶ 10)

Applicants also respectfully disagree with the Examiner's characterization of the data resulting from Assay 93. More specifically, in the outstanding Office Action, the Examiner

alleged that with respect to the positive results observed with PRO444, "one skilled in the art would not attribute the induction of c-fos expression in pericytes by [PRO444] as a physiological reaction specifically induced by [PRO444]." (Final Office Action, August 24, 2004, page 5). On the contrary, Assay 93 included both positive and negative test controls: DME + 5% serum +/- PDGF and buffer respectively. (Declaration ¶ 8) The use of these controls ensured that the resulting data were attributed to the specifically tested compounds (*e.g.,* PRO444), as opposed to some other factor or stimulus. (Declaration ¶ 8) Accordingly, a skilled artisan would readily have attributed the detected c-fos induction specifically to the PRO444 polypeptide. (Declaration ¶ 8)

Applicants emphasize that 35 U.S.C. §101 only requires the application to have *one* asserted "specific, substantial, and credible utility" or a "well-established utility." *See* Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001). Accordingly, if the Examiner finds that PRO444 polypeptides have substantial, specific and credible utility in any of the three utilities asserted and discussed herein (*e.g.,* treating or diagnosing tumors, or stimulating angiogenesis), this rejection must be withdrawn.

Conclusion

The arguments presented herein and the attached Declaration of Dr. Mary Gerritsen clearly show that the claimed invention does have specific, substantial, and credible utility. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made in the specification and herein that set forth the expressly stated utilities of the claimed PRO444 polypeptides.

Thus, given the totality of the evidence provided, Applicants submit that they have established a specific and substantial, credible utility for the claimed PRO444 polypeptides either as diagnostic or therapeutic agents associated with cancer, or for stimulating angiogenesis. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed PRO444 polypeptides set forth in the specification. In view of the above,

Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO also rejected Claims 40-47 and 50-52 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the PTO tied this rejection to the 35 U.S.C. §101 rejection, set forth above, and argued that since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully assert that the arguments made herein and the attached Declaration of Dr. Mary Gerritsen make clear that the claimed PRO444 polypeptides are useful in diagnosing and treating cancer, and inducing angiogenesis in a subject in need. In light of PRO444's demonstrated ability to stimulate c-fos expression, each of the asserted utilities is specific, substantial, and credible. Accordingly, the specification teaches a sufficient utility such that a skilled artisan could make and use the claimed inventions without undue experimentation. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112 – Written Description

The PTO rejected Claims 40-44, 51 and 52 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the PTO alleged that Claims 40-44, directed to polypeptides having at least 80%, 85%, 90%, 95%, or 99% sequence identity with a polypeptide of SEQ ID NO: 9, and Claims 51 and 52, directed to chimeric polypeptides, claim too broad of a genus because there is no disclosed correlation between any particular conserved structure and recited functional limitations.

Applicants respectfully disagree. The claims are directed to polypeptides having a particular structure and are able to induce c-fos expression. Accordingly, skilled practitioners in the art could run a polypeptide having the claimed structure through an assay similar to Assay 93 (disclosed in Example 60 on page 142 of the specification) to determine whether the polypeptide in question was able to induce c-fos expression. As described in our arguments above and in Dr. Gerritsen's attached declaration, the use of positive and negative controls in Assay 93 ensured that the observed c-fos induction was attributed to the particular compound that was tested, and not some other external stimulus. (Declaration ¶ 8) In light of the detailed specification regarding polypeptide sequence identity, chimeric polypeptides, and the protocol of Assay 93, those with skill in the art would readily understand that Applicants had possession of the claimed polypeptides. *See* Specification page 33, lines 4-20, page 40, lines 3-8, page 75, lines 33-37, and page 76, lines 1-3. For these reasons, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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